Biological evaluation of 4-thiazolidinones from 2-hydroxy-1-naphthaldehyde and amino-acid Schiff bases

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Abstract

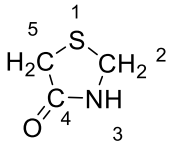
The *in vitro* antimicrobial and antioxidant activities of 4-thiazolidinones synthesized from Schiff bases (3a – 3d) of 2-hydroxy-1-naphthaldehyde and amino acids were evaluated. The bacterial stains of *Staphyloccus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli* and the fungal stains of *Aspergillus niger*, *Aspergillus fumigates* and *Candida albicans* were used for the evaluation.

1. Introduction

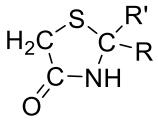
Infectious diseases are responsible for a significant proportion of deaths worldwide and according to the World Health Organization, antimicrobial agents are considered to be "miracle drugs" that are the leading weapons in the treatment of infectious diseases. Unfortunately, a number of the current clinically active antimicrobial agents are becoming less effective because of the development of microbial resistance.

Nitrogen, sulphur and oxygen containing heterocyclic compounds are of countless reputation since a long-time due to their wide spread medicinal properties. In drug industry, the use of thiazole and its derivatives is indispensable. Thiazole ring is present in as such or in another form in Vitamin B_1, promizole and thiabendazole etc. In particular, 4-thiazolidinones have been reported to possess numerous biological activities like antimicrobial [1], anti-inflammatory [2], anti-HIV [3], antiviral [4] and anti-convulsant [5]. Hence, it was envisioned that compounds of 4-thiazolidinones incorporated with Schiff bases have varying biological activities.

The derivatives of thiazolidine with a carbonyl group in the 4-position are called 4-thiazolidinones and are belong to an important group of heterocyclic compounds.



(i)



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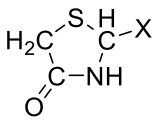


X = O, S, NR or NN=CRR'

(iii)

The numbering of thiazolidinones start from sulphur and follows the general rule. Substituents in 2,3 and 5-positions may be varied but the greatest difference in structure and properties of thiazolidinones is employed by the groups attached to the carbon of the 2-position. If the substituent in position-2 of the structure (iii) is oxygen, the compound is called as 2,4-thiazolidinone, if it is sulphur, the compound is called as rhodanine, if it is imino (NR), the compound is termed as pseudothiohydantoin and if the substituent in position-2 is hydrazino (NN=CRR'), it is named as 4-oxo-2-thiazolin-2-ylhydrazones of the aldehyde or ketone.

Simple and facile synthesis has been employed for the synthesis of the titled derivatives and it was previously reported by us (*J. Chem. and Chemical Sci.*, **7(5)**, 408 - 413, 2017) [6]. It includes, elimination of simple molecules from the substrates by condensation and uncomplicated cyclocondensation to afford the 5-membered heterocyclic derivatives.

Since 4-thiazolidinones are the key pharmacophore of most vital antibiotics, many research articles and investigations were magnificently carried out in decades by the chemists and scholars. It has typical biological properties includes antimicrobial, anti-inflammatory, anti-HIV, antiviral and anticonvulsant. Looking to the biological importance of 4-thiazolidinones, we report here the evaluation of the antimicrobial properties of the synthesized derivatives.

2. Experimental

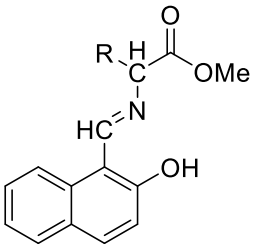
2.1. Screening of antimicrobial activity

Two screening methods [7,8] were employed to analyze and compare the antimicrobial properties of the synthesized compounds. They are,

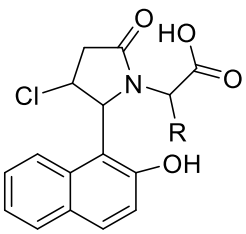
i) Disk diffusion method, and

ii) Serial dilution method

The detailed experimental procedure for these methods were given in our previous article. [9]



3a-3d



4a-4d

R = $(CH_2)_3$, CH_2, -CH-$(CH_3)_2$-CH-, C_6H_5-CH-

3. Results & Discussion

3.1. Antimicrobial activity of compounds by Disc diffusion method

The synthesized compounds (4a – 4d) were evaluated for their active *in vitro* antimicrobial properties against Gram-positive bacterial stains: *Staphylococcus aureus*, *Bacillus subtilis*, Gram-negative stains: *Pseudomonas aeruginosa*, *Escherichia coli*, and the Fungal stains: *Aspergillus niger*, *Aspergillus fumigates*, *Candida albicans* by disk diffusion method. The results were documented for each compound in terms of average diameter of inhibition zones (IZ) in mm. The reference drug ampicillin trihydrate (50 mg) dissolved in 1 ml of DMSO was used in each plate as reference standard.

The results given in Table-1 showed that, the compounds 3a-3d have only feeble inhibitory activity against the microorganisms. The fact is that, the electron withdrawing groups cause the increased inhibitory activity. The compounds 3a-3d having electron donating alkyl groups, and it results decrease in the antimicrobial activity of the compounds considerably. Whereas, the titled derivatives 4a-4d, compared to the free Schiff bases, have showed good to moderate antimicrobial activity. The elevated antimicrobial activity of these compounds is due to the presence of electron withdrawing groups and atoms in these compounds.

Table - 1

Antimicrobial activity of compounds 3a-3d and 4a-4d (DDM)

Entry	Zone of inhibition (mm)						
	Bacterial stains				Fungal stains		
	S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*A. niger*	*A. fumigates*	*C. albicans*
3a	12	14	15	11	13	11	12
3b	11	13	13	10	11	12	13
3c	09	09	10	11	09	10	11
3d	10	11	13	10	12	11	10
4a	12	14	15	12	13	16	17
4b	14	15	13	14	16	14	16
4c	15	13	13	15	14	15	15
4d	22	25	21	23	20	20	20
Ampicillin trihydrate	29	26	28	28	26	21	25
DMSO	00	00	00	00	00	00	00

3.2. Antimicrobial activity of compounds by Serial dilution method

The antimicrobial activity of the synthesized derivatives was evaluated by using serial dilution method. The bacterial stains *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and the fungal stains *Aspergillus niger*, *Aspergillus fumigates* and *Candida albicans* were used to evaluate the inhibitory activity. The microbial activities were assessed by Minimum Inhibitory Concentration (MIC). Noroxin was used as reference for evaluating antibacterial properties and Miconazole was used as reference for evaluating antifungal properties of the synthesized compounds.

The results given in Table-2 showed that, the Schiff base 3d exhibit moderate antibacterial activity with MIC 12.5 µg/ml against the bacterial stain *E. coli* and the fungal stain *A. niger*. The remaining Schiff bases (3a-3c) were exhibited a mild activity. While, the synthesized derivative 4d exhibit good antibacterial activity with MIC 6.25 µg/ml against the bacterial stains *S. aureus*, and the fungal stain *A. niger*, *A. fumigates* and *C. albicans*

Table - 2

Antimicrobial activity of compounds 3a-3d and 4a-4d (SDM)

Entry	MIC (µg/ml)					
		Bacterial stains		Fungal stains		
	S. aureus	***P. aeruginosa***	***E. coli***	***A. niger***	***A. fumigates***	***C. albicans***
3a	25	25	25	50	25	50
3b	50	25	50	50	25	50
3c	25	50	50	50	100	100
3d	25	25	12.5	12.5	25	25
4a	6.25	25	25	12.5	12.5	12.5
4b	25	12.5	12.5	6.25	12.5	25
4c	12.5	12.5	12.5	12.5	25	12.5
4d	6.25	12.5	12.5	6.25	6.25	6.25
Noroxin	6.25	6.25	6.25	-	-	-
Miconazole	-	-	-	6.25	6.25	6.25

4. Conclusion

Based on the above findings, it was concluded that the synthesized compounds possess antibacterial, antifungal, antimycobacterial and antioxidant properties. The introduction / extension of alkyl groups / resonance conjugation of S of 4-thiazolidinones enhances the antimicrobial activity of the derivatives.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the article 'A facile and potent synthesis of 4-thiazolidinones from 2-hydroxy-1-naphthaldehyde and amino acid based Schiff bases'

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